Oxidative Rearrangement of 2-Substituted Oxazolines. A Novel Entry to 5,6-Dihydro-2*H*-1,4-oxazin-2-ones and Morpholin-2-ones

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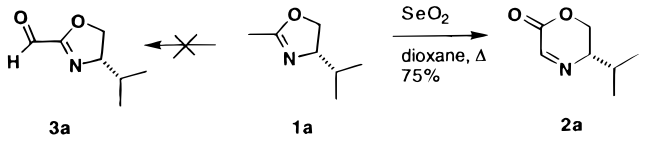
A novel synthesis of 5,6-dihydro-2*H*-1,4-oxazin-2-ones by SeO_2-promoted oxidative rearrangement of 2-alkyl- and 2-(arylmethyl)oxazolines is described. Yields are good to excellent (up to 94%) with the highest yields obtained for 2-arylmethyl- and 2-neopentyl-substituted oxazolines. This reaction provides convenient access to novel 5-aryl-substituted dihydrooxazinones in high yield. The latter compounds are important "chiral glycine" synthons for asymmetric synthesis of α-amino acids. Since oxazolines are readily derived from carboxylic acids or their equivalents, this oxidative rearrangement constitutes an entry to synthesis of α-amino acids from carboxylic acids. A mechanism is proposed to account for the rearrangement involving a "nitrilium to acylium" 1,2-migration.

In the course of preparation of intermediates for the synthesis of antifungal marine natural products we discovered an unexpected oxidative rearrangement in the SeO_2-promoted oxidation of 2-substituted oxazolines, **1**. This novel reverse-Beckmann type rearrangement occurred after oxidation of the α-carbon of **1** by SeO_2 with subsequent *β*-cleavage by 1,2-migration and concomitant ring expansion. The molecular rearrangement was exploited for the synthesis of 3-substituted 5,6-dihydro-2*H*-1,4-oxazin-2-ones (**2**) from oxazolines and preparation of previously inaccessible 3-*unsubstituted* derivatives. The latter are readily converted to tetrahydro-1,4-oxazin-2-ones (**4**, morpholinones). Both **2** and **4** are useful chiral glycine synthons.[2−7] Since **4b** has been used in efficient syntheses of α-amino acids with high %ee[2,3,7] and oxazolines are readily derived from alkylimidates (carboxylic acid equivalents), the oxidative rearrangement described here constitutes a novel asymmetric synthesis of α-amino acids from carboxylic acids.

Results

Heating a solution of oxazoline **1a**, $C_7H_{13}NO$, in dioxane with selenium dioxide (2.2 equiv) at reflux resulted in efficient conversion to a single, less polar product (TLC) which was isolated after nonaqueous workup. The product formula, $C_7H_{11}NO_2$ (HREIMS, *m*/*z* 141.0785, Δmmu 0.5) clearly showed oxidation of **1a** had taken place; however, the structure was that of dihydrooxazinone **2a** (75% isolated yield) and not the anticipated isomeric 2-formyloxazoline **3a**. The C2 methyl signal of **1a** had been replaced in the ^{1}H NMR spectrum of **2a** by a vinyl proton signal (*δ* 7.87, d, J = 2.8 Hz) which was now allylically coupled to the *N*-CH (*δ* 3.48, ^4J = 2.8 Hz). The IR spectrum revealed the presence of an ester carbonyl (*ν* 1748 cm^{-1}) and an imine double bond (1631 cm^{-1}) which were further corroborated by ^{13}C NMR (*δ* 154.5, s, C=O; 152.2, d, $^1J_{CH}$ 193 Hz, CH=N). The exceptionally high-field ^{13}C signal for the α,*β*-unsaturated azalactone carbonyl is characteristic of dihydro-2*H*-1,4-oxazin-2-ones.[8] Catalytic hydrogenation of **2a** (1 atm, H_2, Pd−C, Scheme 1) gave morpholin-2-one **4a** ((5*S*)-5-isopropyl-3,4,5,6-tetrahydro-1,4-oxazin-2-one, *m*/*z* 143.0944, Δmmu 0.2) as a ninhydrin-positive secondary amine. The spectroscopic data of **4a** (^{1}H NMR, ^{13}C NMR) compared well with literature values for related morpholin-2-ones.[3,5] Thus, the product of oxidation of oxazoline **1a** was shown to be the rearranged heterocycle **2a**.



The scope of the SeO_2-mediated oxidative rearrangement of substituted oxazolines was investigated (Table 1). It was found that the ease of the oxidative rearrangement correlated with the migratory aptitude of the R substituent (Table 1) in the postulated 2-acyl intermediate **3** (see Discussion). The yields were highest when R was H, aryl or *tert*-alkyl (e.g. **1i**, entry 12, 94%, the naphthyl isomers **1k**, entry 83%, and **1l**, entry 14, 93%, respectively, and the 2-neopentyl derivative **1h**, entry 10, 84%). The yield was lower for tertiary R (**1g**, 33%, entry 9), and 2- ethyl oxazolines (R = Me) did not undergo the reaction at all, but gave oxidized byproducts which were tentatively assigned structures **5f** and *epi*-**5f** (∼40% combined, entry 8). The best yields of **2** from 2-methyloxazolines were obtained for compounds substituted at C4 with secondary alkyl or aryl groups (**2a**, entry 1, 75%; **2b**, entry 4, 72%). The C4 oxymethylene-substituted oxazolines **1c**,**d** (entries 5 and 6) were also converted to the corresponding oxazinones **2c**,**d**, respectively, albeit in lower yields (22% and 53%, respectively), possibly due to competing side chain oxidation. The "parent" oxazoline **1e** (entry 7) was oxidized with difficulty by SeO_2 to the simple, undescribed oxazinone **2e** (*m*/*z* 99) and in

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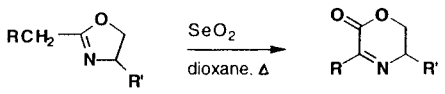
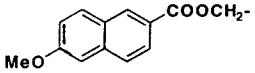
Table 1. SeO_2-Promoted Oxidative Rearrangement of 2-Substituted Oxazolines

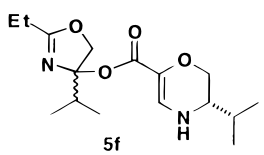


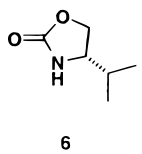
1 2

Entry	Oxazoline (1)	C4 of 1	R	R'	Yield (%)[a]	Product (2)
1	**1a**	*S*	H	*i*-Pr	75	**2a**
2	**1a**	*S*	H	*i*-Pr	58[b]	**2a**
3	**1a**	*S*	H	*i*-Pr	0[c, d]	-
4	**1b**	*R*	H	Ph	72	**2b**
5	**1c**	*R*	H	$BnOCH_2$-	22	**2c**
6	**1d**	*S*	H		53	**2d**
7	**1e**	-	H	H	60[e]	**2e**
8	**1f**	*S*	Me	*i*-Pr	0[f]	**2f**
9	**1g**	*S*	*i*-Pr	*i*-Pr	33	**2g**
10	**1h**	*R*	*t*-Bu	Ph	84	**2h**
11	**1i**	*R*	Ph	Ph	94	**2i**
12	**1j**	*S*	Ph	*i*-Pr	74	**2j**
13	**1k**	*R*	1-naphthyl	Ph	83	**2k**
14	**1l**	*R*	2-naphthyl	Ph	93	**2l**

(a) Yield of isolated product. Each new compound gave satisfactory HRMS and/or elemental analysis (except **2e**),IR, ^1H NMR and ^{13}C NMR; (b) solvent was THF; (c) Isolated product was 4-isopropyloxazolidinone **6**; (d) carried out in pyridine; (e) GC yield. Product **2e** was detected by GCMS (*m/z* 99, M^+) and ^1H NMR (δ 7.88, t, 1H, CH=N, *J*= 2.3 Hz); (f) Only dimeric products **5f** and *epi*-**5f** were isolated in low yield (*ca.* 40%).

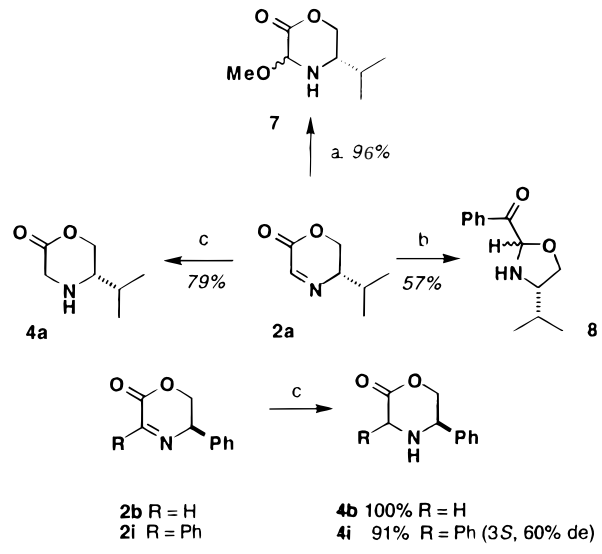
lower yield (60% by GC). Reaction of **1a** in refluxing THF (67 °C) also gave **2a**; however, the reaction proceeded sluggishly with diminished yield (58%, entry 2). Oxidation of **1a** with SeO_2 in refluxing pyridine (entry 3) gave only traces of dihydrooxazinone **2a** with the only other isolable product being oxazolidinone **6**,[9] arising from competitive oxidative carbon−carbon bond cleavage of the putative formyl intermediate **3a**.





To the best of our knowledge, 3-*unsubstituted* 5,6-dihydro-2*H*-1,4-oxazin-2-ones are unknown in the literature so we briefly examined the chemical properties of **2** (Scheme 1). Dihydrooxazinone **2a** is sensitive to water and other hydroxylic solvents. Heating with methanol at reflux gave a 96% yield of epimeric 3-methoxymorpholin-2-ones, **7** (1:1). Addition of phenyllithium to **2a** (−78 °C, THF, 20 min) gave the substituted epimeric

Scheme 1[a]

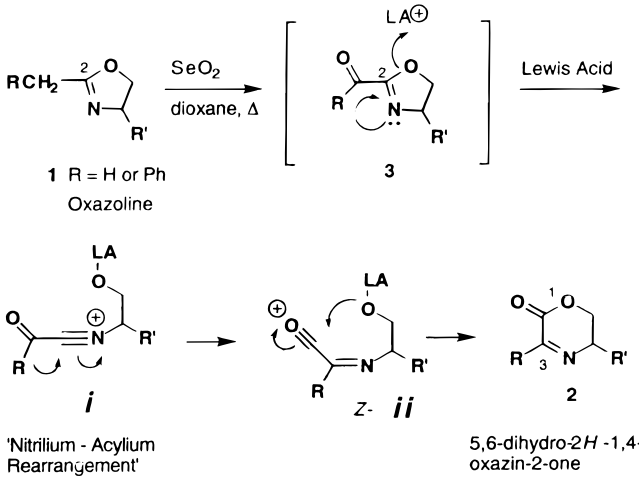


[a] (a) MeOH, 60 °C; (b) PhMgBr, THF, −78 °C; (c) H_2, Pd−C.

2-benzoyloxazolidines **8** by nucleophilic attack at the carbonyl group and subsequent ring closure by intramolecular addition of the liberated alkoxide to the 3,4-imine

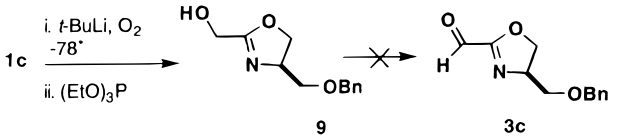
(9) Evans, D. A.; Mathre, D. J.; Scott, W. L. *J. Org. Chem.* **1985**, *50*, 1830−1835.

Scheme 2



double bond. Brief catalytic hydrogenation of the imine bond (1 atm, H_2, Pd−C) in derivatives **2a** and **2b** was quantitative and proceeded without hydrogenolysis of the benzylic carbon in **2b**. Conversion of **1i** to **2i** was achieved without detectable racemization at C5 as shown by chiral lanthanide reagent-induced shifts in the ^{1}H NMR spectrum of (−)-**2i**. Resolution of the ^{1}H NMR signals of (±)-**2i** was achieved with (+)-Eu(hfc)$_3$; however, only one set of signals were detected in (−)-**2i** (>99% ee).

Ether solvents, such as dioxane, that promote Lewis acid-catalyzed ionic mechanisms favored high yields, possibly by stabilization of incipient cationic intermediates prior to rearrangement. Conversely, the oxidative rearrangement of **1a** fails when carried out in pyridine, giving oxazolidinone **6** instead (entry 3). 2-Formyloxazolines **3** could not be isolated and, in fact, appear to be inherently unstable. Several attempts to prepare **3c** by oxidation (MnO_2, Swern oxidation, TPAP or PDC) of 2-(hydroxymethyl)oxazoline **9**, prepared by an independent route (i. *t*-BuLi, −78 °C, THF, ii. O_2, iii. $(EtO)_3P$[10]), were unsuccessful and returned only mixtures of products, occasionally containing **2c** (∼10%, ^{1}H NMR).



Discussion

We propose a mechanism for the SeO_2-promoted formation of dihydrooxazinone **2** that proceeds through a Lewis acid-catalyzed rearrangement of a 2-acyloxazoline intermediate **3** (Scheme 2). α-Keto carbonyl compounds are formed by SeO_2 oxidation of carbonyl compounds and their derivatives,[11] and by analogy, 2-acyloxazoline **3** is a reasonable intermediate in the oxidation of **2**. In the presence of Lewis acid, compound **3** is unstable and undergoes rapid Lewis acid-catalyzed ring opening leading to the conjugated nitrilium ion *i*. The sources of Lewis acid may be selenium-containing byproducts formed during reduction of SeO_2. Cationic *i* then rearranges by a 1,2-shift to acylium ion *ii* followed by ring closure to afford dihydrooxazinone **2**. The nucleophilic 1,2-migration of group R (Scheme 2) in the oxidative rearrangement is invoked here to account for exchange of oxidation states between C2 and the 2-acyl substituent of the intermediate **3** (oxazoline numbering). Because the C2 carbon of oxazoline is equivalent to a carboxamide, the rearrangement is, formally, the *reverse* of the Beckmann rearrangement in which 1,2-migration from the α-position of activated oxime generates a iminium carbocation (nitrilium ion).[12,13] The SeO_2-promoted oxidative rearrangement of oxazolines appears to be a rare example of rearrangement of a nitrilium ion to give an imine. The fission of a relatively strong sp^2 carbon−carbon σ bond in the rearrangement step **i** to **ii** may be partially compensated by stabilization imparted to the intermediate *ii* by sp−sp^2 rehybridization of nitrogen and oxygen. Solvent participation appears to be important and may contribute to stabilization of putative ionic intermediates *via* covalent dioxane adducts; however, further study of the mechanism is required to clarify the details.

SeO_2-promoted oxidative rearrangement of **1** to **2** is useful in the synthesis of optically active α-amino acids. Although 3-substituted dihydro-2*H*-1,4-oxazinones are known,[14] the 3-*unsubstituted* analogs of **2** have not been reported previously and represent new, potentially useful chiral glycine synthons. The more familiar morpholin-2-one **4b** has been utilized in synthesis of α-amino acids by stereoselective alkylation[2,3] and the synthesis of β-hydroxy-substituted amino acids via azomethine ylides,[6,7] while the 6-phenyl derivative of **4b** has been employed in α-amino acid synthesis as an "electrophilic glycinate".[15] The best current preparation of **4b** (condensation of phenylglycinol with phenyl α-bromoacetate)[3] is reported to suffer from variable yields (40−83%) and is prone to dimerization of the product. Because dihydro-2*H*-oxazinones **2** are readily converted to **4**, the SeO_2 oxidative rearrangement makes **4b** conveniently accessible from oxazolines, which in turn are easily prepared from the corresponding 2-amino alcohols.[16] Thus, oxazoline **1b** prepared by condensation of *R*-(−)-phenylglycinol with ethyl acetimidate hydrochloride (Et_3N, CH_2Cl_2, 91%), was smoothly converted to **2b** (SeO_2, reflux, 1.5 h, dioxane, 72%, Table 1, entry 4). Hydrogenation of **2b** (H_2, 1 atm, Pd−C, 3 h, quantitative, Scheme 1) afforded optically pure (−)-morpholinone **4b** in an overall *reproducible* yield of 66% in three steps from phenylglycinol. By an analogous sequence, **2i** was hydrogenated to the known (3*S*,5*R*)-3,5-diphenylmorpholinone **4i** (91%, 60% de) in 74% overall yield from α-phenylacetimidate hydrochloride and (*R*)-(−)-phenylglycinol.

The utility of this novel reaction was demonstrated by a simple asymmetric synthesis of the amino acid (*S*) *tert*-leucine (*tert*-butylglycine, **10**, Scheme 3), a component of natural product peptides isolated from marine sponges of the genus *Theonella*.[17,18] The chiral auxillary (*R*)-2-phenylglycinol was readily condensed with *tert*-butylacetyl chloride in two steps to provide oxazoline **1h**.[19] Oxazoline **1h** was smoothly converted to **2h** with SeO_2

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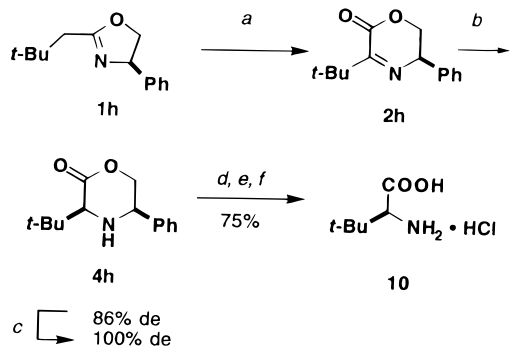
Scheme 3[a]



[a] (a) SeO_2, diox, Δ; (b) H_2, 1 atm, PtO_2, CH_2Cl_2; (c) recryst, EA/hex; (d) EtOH, HCl; (e) H_2, 1 atm, Pd−C, EtOH; (f) 6 M HCl aqueous.

in refluxing dioxane (84%, Table 1, entry 10). Hydrogenation of **2h** using Harwood's conditions (PtO_2, CH_2Cl_2, 1 atm H_2),[5] gave the desired (2*S*,4*R*) morpholinone diastereomer **4h** (97%, de 86%) which was improved to de 99% (82% yield) after recrystallization from ethyl acetate−hexane. Ethanolysis of diasteromerically pure **4h** (HCl, EtOH) followed by sequential hydrogenolysis of the phenylglycinol group[3] and acid hydrolysis (6 N HCl aqueous) provided (*S*)-(−)-**10** (75%, from **4h**), identical with an authentic sample by ^{1}H NMR, $[\alpha]_D$, and TLC, and optically pure as determined by Marfey's method.[20]

We expect that the new 3-unsubstituted dihydro-2*H*-oxazinones, in particular **2b**, will find utility in α-amino acid synthesis as electrophilic chiral glycine equivalents.[21] It is noteworthy that SeO_2-mediated oxidative rearrangement of oxazolines provides entry to synthesis of heavily *β*-branched α-amino acids in high optical purity and complements recently reported catalytic methods, such as the asymmetric Strecker synthesis[22] and supercritical homogeneous catalytic hydrogenation of α-enamides.[23] Other potential uses of 3-unsubstituted oxazinones may include heterocyclic synthesis *via* hetero-Diels−Alder cycloaddition with suitable dienes[24] or 1,3-dipolar additions of derived azamethine ylides.[7] Further studies of the mechanism of this oxidative rearrangement and its synthetic applications are underway in our laboratory.

Experimental Section

General Experimental. THF and 1,4-dioxane were purified by distillation from sodium−benzophenone ketyl. ^{1}H and ^{13}C NMR were recorded at 300 and 75 MHz, respectively. Homonuclear *J* couplings were confirmed by COSY or single-frequency decoupling experiments. ^{13}C NMR signal chemical shift and multiplicity assignments (CH_3, methyl; CH_2, methylene; CH, methine; C, quaternary) were made from DEPT, HETCOR, and HMBC spectra. GCMS was carried out on a capillary column (silicone coating) coupled to an ion-trap mass detector. High resolution mass spectra were provided by the University of Minnesota Mass Spectrometry Laboratory. Other procedures are described elsewhere.[25]

General Preparation of Oxazolines. 2-Methyloxazoline and ethyl acetimidate hydrochloride were purchased from the Aldrich Chemical Co. Oxazolines were prepared according to one of three methods. Method A: Condensation of ethyl acetimidate hydrochloride with (*S*)-(+)-valinol (**1a**, 78%[26]) or (*R*)-(−)-phenylglycinol (**1b**, 91%) according to Meyers.[16] Method B: Condensation of (*S*)-valinol or (*R*)-(−)-phenylglycinol with ethyl propionimidate hydrochloride (**1f**),[27] or ethyl α-phenylacetimidate hydrochloride (**1i**, 87%;[28] **1j**, 78%), or 1-naphthylacetimidate (**1k**, 91%) or 2-naphthylacetimidate hydrochloride (**1l**, 49%). Arylacetimidate hydrochlorides were prepared by bubbling dry HCl into cold ethanolic solutions of the corresponding arylacetonitriles.[27] Method C: Condensation of acid chloride with (*S*)-valinol or (*R*)-(−)-phenylglycinol followed by dehydration of the product amide with $SOCl_2$ and Et_3N in CH_2Cl_2.[19] Other oxazolines were prepared by alkylation (**1c**, NaH, $ArCH_2Br$, THF) or acylation (**1d**, $ArCO_2H$, DCC, Et_3N, THF) of (*R*)-4-(hydroxymethyl)-2-methyloxazoline, obtained from (*S*)-serine ethyl ester hydrochloride.[29]

(4*S*)-2-(2-Methylpropyl)-4-isopropyl-4,5-dihydrooxazole (1g). Method C: A solution of (*S*)-valinol (3.00 g, 29.1 mmol) in CH_2Cl_2 (20 mL) was added to solution of isovaleroyl chloride (3.4 mL, 32.5 mmol) in CH_2Cl_2 (50 mL). Triethylamine (4.6 mL, 33.0 mmol) was added, and the solution was stirred overnight. The reaction mixture was poured into NH_4Cl (15 mL, aqueous, saturated) and H_2O (30 mL). The aqueous layer was extracted 2 × 300 mL of Et_2O. The Et_2O was dried through $MgSO_4$ and reduced to a clear colorless oil (5.49 g) which crystallized upon standing. The amide alcohol (5.49 g, 29.0 mmol) was then dissolved in CH_2Cl_2 (150 mL) to which thionyl chloride (8.6 mL, 118 mmol) was added at 0 °C. After 3.5 h, the solvent and excess thionyl chloride was removed *in vacuo*. The crude material was dissolved in Et_2O (400 mL), and 35 mL of saturated $NaHCO_3$, 35 mL of H_2O, and 23 mL of 3 M NaOH were added. This mixture stirred for 0.5 h. Then the layers were separated, and the aqueous layer was extracted with Et_2O (400 mL). The Et_2O layers were dried through $MgSO_4$ and reduced to a yellow oil (5.51 g) The crude mixture was purified by bulb-to-bulb distillation (125 °C, 0.9 torr) to give 2.44 g (50%) of a clear, colorless oil. $[\alpha]_D = -56.0°$ (*c* 5.42, CH_3CN); IR (NaCl, neat) 1643 cm^{-1} (C=N); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 0.81 (d, 3 H, *J* = 6.8 Hz), 0.892 (d, 3 H, *J* = 6.8 Hz), 0.895 (d, 3 H, *J* = 6.6 Hz), 0.90 (d, 3 H, *J* = 6.6 Hz), 1.68 (ddq, 1 H, *J* = 6.8 Hz), 1.96 (dq, 1 H, *J* = 6.6 Hz), 2.10 (d, 2 H, *J* = 6.8 Hz), 3.84 (m, 2 H), 4.13 (m, 1 H); ^{13}C NMR ($CDCl_3$) *δ* 18.0 (CH_3), 18.6 (CH_3), 22.3 (2 × CH_3), 26.2 (CH), 32.4 (CH), 37.0 (CH_2), 69.5 (CH_2), 71.9 (CH), 166.6 (C); HREIMS found *m*/*z* 169.1462 (M^+), $C_{10}H_{19}NO$ requires 169.1467.

(4*R*)-2-(2,2-Dimethylpropyl)-4-phenyl-4,5-dihydrooxazole (1h). Method C: oil, 51%. $[\alpha]_D = +34.0°$ (*c* 4.46, $CHCl_3$); IR (NaCl, neat) 1661 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$) *δ* 1.08 (s, 9 H), 2.32 (s, 2 H), 4.05 (dd, 1 H, *J* = 8.5, 8.5 Hz), 4.60 (dd, 1 H, *J* = 10.2, 8.5 Hz), 5.19 (dd, 1 H, *J* = 10.2, 8.5 Hz), 7.27 (m, 5 H); ^{13}C NMR ($CDCl_3$) *δ* 29.6 (CH_3), 30.7 (C), 41.6 (CH_2), 69.4 (CH), 74.1 (CH_2), 126.4 (2 × CH), 127.2 (CH), 128.4 (2 × CH), 142.4 (C), 167.4 (C); HREIMS found *m*/*z* 217.1464 (M^+), $C_{14}H_{19}NO$ requires 217.1467.

(4*S*)-2-Benzyl-4-isopropyl-4,5-dihydrooxazole (1j). Method B: clear oil, 78%; $R_f = 0.26$, 3:7 ethyl acetate:hexane. IR (NaCl, neat) 1669 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$) *δ* 0.85 (d, 3 H, *J* = 6.8 Hz), 0.94 (d, 3 H, *J* = 6.8 Hz), 1.72 (dq, 1 H, *J* = 6.8 Hz), 3.60 (s, 2 H), 3.87 (m, 2 H), 4.14 (m, 1 H), 7.29 (m, 5 H); ^{13}C NMR ($CDCl_3$) *δ* 17.8 (CH_3), 18.4 (CH_3), 32.3 (CH), 34.6 (CH_2), 69.9 (CH_2), 71.8 (CH), 126.6 (CH), 128.2 (2 × CH), 128.6 (2 × CH), 135.1 (C), 165.3 (C); HREIMS found *m*/*z* 203.1311 (M^+), $C_{13}H_{17}NO$ requires 203.1310.

(4*R*)-2-(1-Naphthylmethyl)-4-phenyl-4,5-dihydrooxazole (1k). Method B: Triethylamine (5.2 mL, 37.3 mmol) was

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added dropwise to a stirred mixture of (*R*)-(−)-2-phenylglycinol (3.94 g, 28.7 mmol), ethyl 1-naphthylacetimidate hydrochloride (8.60 g, 34.5 mmol), and CH_2Cl_2 (144 mL). After stirring at room temperature overnight, the reaction mixture was poured into ice−water, and the aqueous layer was extracted three times with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and reduced *in vacuo* to an opaque, viscous oil (8.58 g). Baseline impurities were removed by column chromatography (silica gel, 3:7 ethyl acetate:hexane) to give **1k** as a yellow solid (5.94 g, 91%; R_f = 0.18, 3:7 ethyl acetate:hexane). Mp 57−59 °C; $[\alpha]_D$ = +62.6° (*c* 4.65, $CHCl_3$); UV (acetonitrile) 225 (ϵ 44670), 271 (5870), 281 (6970), 288 (4700), 291 (4680), 313 nm (220); IR (NaCl, neat) 1662 cm^{-1} (C═N); ^1H NMR ($CDCl_3$) δ 3.93 (dd, 1 H, *J* = 8.5, 8.1 Hz), 4.14 (s, 2 H), 4.43 (dd, 1 H, *J* = 10.1, 8.5 Hz), 5.10 (dd, 1 H, *J* = 10.1, 8.1 Hz), 7.19 (m, 5 H), 7.43 (m, 4 H), 7.74 (d, 1 H, *J* = 8.1), 7.80 (dd, 1 H, *J* = 7.6, 1.3 Hz), 8.22 (d, 1 H, *J* = 8.6 Hz); ^{13}C NMR ($CDCl_3$) δ 32.6 (CH_2), 69.5 (CH), 74.7 (CH_2), 124.0 (CH), 125.3 (CH), 125.6 (CH), 126.0 (CH), 126.4 (CH), 127.3 (CH), 127.5 (CH), 127.8 (CH), 128.4 (2 × CH), 128.5 (CH), 131.2 (C), 131.9 (C), 133.7 (C), 142.1 (C), 157.2 (C), 166.9 (C); HREIMS found *m*/*z* 287.1308 (M^+), $C_{20}H_{17}NO$ requires 287.1310.

(4*R*)-2-(2-Naphthylmethyl)-4-phenyl-4,5-dihydrooxazole (1l). Method B: Oxazoline **1l** was prepared (49%) from ethyl 2-naphthylacetimidate hydrochloride in a similar fashion to **1k**: yellow solid, R_f = 0.14, 3:7 ethyl acetate:hexane. Mp 50−50.5 °C; $[\alpha]_D$ = +86.1° (*c* 4.92, $CHCl_3$); UV (acetonitrile) 224 (ϵ 111,000), 267 (6750), 276 (6970), 286 (5250), 366 nm (1950); IR (NaCl, neat) 1666 cm^{-1} (C═N); ^1H NMR ($CDCl_3$) δ 3.82 (s, 2 H), 4.09 (dd, 1 H, *J* = 8.5, 8.2 Hz), 4.60 (dd, 1 H, *J* = 10.0, 8.5 Hz), 5.21 (dd, 1 H, *J* = 10.0, 8.2 Hz), 7.28 (m, 5 H), 7.48 (m, 3 H), 7.82 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 34.8 (CH_2), 69.4 (CH), 74.7 (CH_2), 125.6 (CH), 125.9 (CH), 126.4 (3 × CH), 126.9 (CH), 127.3 (CH), 127.5 (2 × CH), 128.1 (CH), 128.5 (2 × CH), 132.3 (C), 132.5 (C), 133.3 (C), 142.1 (C), 166.9 (C); HREIMS found *m*/*z* 287.1308 (M^+), $C_{20}H_{17}NO$ requires 287.1310.

General Procedure for SeO_2-Promoted Oxidative Rearrangement. (5*S*)-5-Isopropyl-5,6-dihydro-2*H*-1,4-oxazin-2-one (2a). A solution of (4*S*)-oxazoline **1a** (0.101 g, 0.82 mmol)[26] in dry dioxane (2 mL) was added to a suspension of selenium dioxide (0.196 g, 1.77 mmol) in dioxane (2 mL), and the mixture was heated at reflux for 2 h. The mixture was cooled and purified by direct application to a column of silica gel and elution with ethyl acetate to give **2a** as a light-tan oil, essentially pure by ^1H NMR (0.0849 g, 75%), R_f 0.58 (ethyl acetate). Crystallization of **2a** from *n*-hexane at −20 °C gave an analytical sample as long colorless needles: mp 2−3 °C; $[\alpha]_D$ = +97.4° (*c* 0.83, $CHCl_3$); CD (hexane) λ 197 nm ($\Delta\epsilon$ −7.5), 243 (7.8), 291 (-0.1), 335 (0.5); UV (hexane) λ 202 nm (ϵ 13800), 348 (298); IR (NaCl, neat) 1748 (C═O), 1631 (C═N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04 (d, 3 H, *J* = 6.8 Hz, *i*-Pr), 1.06 (d, 3 H, *J* = 6.8 Hz, *i*-Pr), 1.93 (dq, 1 H, *J* = 6.8, 6.8 Hz, *i*-Pr), 3.48 (dddd, 1 H, *J* = 9.5, 6.8, 4.4, 2.8 Hz, H5), 4.24 (dd, 1 H, *J* = 11.7, 9.5 Hz, H6a), 4.45 (dd, 1 H, *J* = 11.7, 4.4 Hz, H6b), 7.87 (d, 1 H, *J* = 2.8 Hz, H3); ^{13}C NMR ($CDCl_3$) δ 18.7 (CH_3), 19.2 (CH_3), 30.4 (CH), 61.5 (CH), 68.3 (CH_2), 152.2 (CH, $^1J_{C-H}$ = 193 Hz, C3), 154.5 (C, C2); HREIMS found *m*/*z* 141.0785 (M^+), $C_7H_{11}NO_2$ requires 141.0790. Anal. Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.21; H, 7.89; N, 9.83.

(5*R*)-5-Phenyl-5,6-dihydro-2*H*-1,4-oxazin-2-one (2b): yellow oil (72%); $[\alpha]_D$ = −252° (*c* 5.23, $CHCl_3$); UV (acetonitrile) λ 212 (ϵ 11200), 240 (1420), 338 (150); IR (NaCl, neat) 1762 (C═O), 1631 (C═N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.28 (dd, 1 H, *J* = 11.7, 10.8 Hz, H6a), 4.61 (dd, 1 H, *J* = 11.7, 4.7 Hz, H6b), 4.91 (ddd, 1 H, *J* = 10.8, 4.7, 3.1 Hz, H5), 7.37 (m, 5 H), 8.06 (d, 1 H, *J* = 3.1 Hz, H-3); ^{13}C NMR ($CDCl_3$) δ 59.5 (CH), 70.6 (CH_2), 126.8 (CH), 128.1 (CH), 128.6 (CH), 136.0 (C), 152.9 (CH, C-3), 153.8 (C); HREIMS found *m*/*z* 175.0634 (M^+), $C_{10}H_9NO_2$ requires 175.0633.

(5*R*)-5-[(Benzyloxy)methyl]-5,6-dihydro-2*H*-1,4-oxazin-2-one (2c): colorless oil (22%); R_f = 0.62 (ethyl acetate); $[\alpha]_D$ = −23.8° (*c* 0.913, $CHCl_3$); IR (NaCl, neat) 1746 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.62 (dd, 1 H, *J* = 9.6, 7.3 Hz), 3.87 (dd, 1 H, *J* = 9.6, 4.2 Hz), 4.00 (m, 1 H), 4.42 (dd, 1 H, *J* = 11.7, 8.4 Hz), 4.57 (dd, 1 H, *J* = 11.7, 4.4 Hz), 4.59 (s, 2 H), 7.35 (m, 5 H), 7.90 (d, 1 H, *J* = 2.6 Hz, H-3); ^{13}C NMR ($CDCl_3$) δ 56.1 (CH), 68.0 (CH_2), 69.0 (CH_2), 73.6 (CH_2), 127.6 (CH), 127.9 (CH), 128.5 (CH), 137.3 (C), 153.5 (CH, $^1J_{C-H}$ = 194 Hz, C-3), 154.3 (C); HRCIMS found *m*/*z* 220.0982 (MH^+), $C_{12}H_{14}NO_3$ requires 220.0974.

(5*S*)-5-[(6′-Methoxy-2′-naphthoyloxy)methyl]-5,6-dihydro-2*H*-1,4-oxazin-2-one (2d): colorless solid (53%); R_f = 0.56 (ethyl acetate); ^1H NMR ($CDCl_3$) δ 3.95 (s, 3 H), 4.26 (m, 1 H), 4.50 (dd, 1 H, *J* = 11.8, 8.6 Hz), 4.57 (dd, 1 H, *J* = 11.6, 6.4 Hz), 4.68 (dd, 1 H, *J* = 11.8, 4.4 Hz), 4.77 (dd, 1 H, *J* = 11.6, 4.5 Hz), 7.15 (d, 1 H, *J* = 2.5 Hz), 7.21 (dd, 1 H, *J* = 8.9, 2.5 Hz), 7.76 (d, 1 H, 8.6 Hz), 7.85 (d, 1 H, 8.9 Hz), 7.97 (dd, 1 H, *J* = 8.6, 1.7 Hz), 7.98 (d, 1 H, *J* = 2.8, H-3), 8.49 (bs, 1 H); ^{13}C NMR ($CDCl_3$) δ 55.3 (CH_3), 55.4 (CH), 63.3 (CH_2), 67.7 (CH_2), 105.7 (CH), 119.8 (CH), 124.0 (C), 125.7 (CH), 127.0 (CH), 127.8 (C), 130.9 (CH), 131.2 (CH), 137.4 (C), 154.0 (CH, C-3), 159.8 (C), 166.3 (C); HREIMS found *m*/*z* 313.0956 (M^+), $C_{17}H_{15}NO_5$ requires 313.0950.

5,6-Dihydro-2*H*-1,4-oxazin-2-one (2e). A solution of 2-methyloxazoline (**1e**, 0.1037 g, 1.22 mmol) and *n*-nonane (10 mol %, internal standard) in dry THF (6 mL) was heated under reflux with SeO_2 (0.2875 g, 2.59 mmol) and the reaction monitored by GCMS. After 1.5 h, the crude mixture was filtered through silica gel and eluted with diethyl ether. Careful evaporation of the eluate under a stream of nitrogen gave a yellow oil (11 mg) containing **2e** that was analyzed by NMR and GCMS. 60% yield by GC; ^1H NMR ($CDCl_3$) δ 3.87, (m, 2H), 4.47 (t, 2H, *J* = 5.5 Hz), 7.88 (t, 1H, CH═N, *J*= 2.3 Hz), ; GCMS, *m*/*z* 99 (M^+), t_R 7.29 min, 50−150 °C @ 4 °C/min, 30 m × 0.32 mm, DB5.

(5*S*)-2,5-Diisopropyl-5,6-dihydro-2*H*-1,4-oxazin-2-one (2g): 33%; R_f = 0.47, 3:7 ethyl acetate:hexane. $[\alpha]_D$ = +89.4° (*c* 3.76, acetonitrile); IR (NaCl, neat) 1738 (C═O), 1637 (C═N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (d, 3 H, *J* = 7.0 Hz), 1.05 (d, 3 H, *J* = 7.0 Hz), 1.13 (d, 3 H, *J* = 6.8 Hz), 1.16 (d, 3 H, *J* = 6.8 Hz), 1.86 (dq, 1 H, *J* = 6.8 Hz), 3.20 (dq, 1 H, *J* = 7.0, 1.3 Hz), 3.40 (dddd, 1 H, *J* = 9.2, 6.8, 4.1, 1.3 Hz), 4.14 (dd, 1 H, *J* = 11.3, 9.2 Hz), 4.39 (dd, 1 H, *J* = 11.3, 4.1 Hz); ^{13}C NMR ($CDCl_3$) δ 18.6 (CH_3), 19.1 (CH_3), 19.3 (CH_3), 20.0 (CH_3), 30.4 (CH), 31.8 (CH), 60.8 (CH), 68.2 (CH_2), 155.6 (C), 165.6 (C); HREIMS found *m*/*z* 183.1255 (M^+), $C_{10}H_{17}NO_2$ requires 183.1259.

(5*R*)-3-*tert*-Butyl-5-phenyl-5,6-dihydro-2*H*-1,4-oxazin-2-one (2h): yellow solid, 84%. Mp 63−65.5 °C; $[\alpha]_D$ = −191.1° (*c* 5.37, $CHCl_3$); IR (NaCl, neat) 1742 (C═O), 1628 (C═N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (s, 9 H), 4.00 (dd, 1 H, *J* = 11.3, 11.0 Hz), 4.45 (dd, 1 H, *J* = 11.3, 4.3 Hz), 4.76 (dd, 1 H, *J* = 11.0, 4.3 Hz), 7.36 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 27.9 (CH_3), 39.1 (C), 59.2 (CH), 71.0 (CH_2), 126.8 (2 × CH), 127.9 (CH), 128.6 (2 × CH), 137.0 (C), 154.0 (C), 168.5 (C); HREIMS found *m*/*z* 231.1257 (M^+), $C_{14}H_{17}NO_2$ requires 231.1259.

(5*R*)-3,5-Diphenyl-5,6-dihydro-2*H*-1,4-oxazin-2-one (2i): yellow oil (94%); R_f = 0.68 (ethyl acetate); $[\alpha]_D$ = −351° (*c* 3.96, $CHCl_3$); UV (acetonitrile) λ 210 (ϵ 20700), 265 (7500), 366 (210); IR (NaCl, neat) 1746 (C═O), 1609 (C═N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.25 (dd, 1 H, *J* = 11.3, 10.8 Hz), 4.59 (dd, 1 H, *J* = 11.3, 4.4 Hz), 4.98 (dd, 1 H, *J* = 10.8, 4.4 Hz), 7.40 (m, 8 H), 8.08 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 60.1 (CH), 71.2 (CH_2), 127.1 (CH), 128.1 (CH), 128.2 (CH), 128.8 (2 × CH), 131.2 (CH), 133.9 (C), 136.8 (C), 154.8 (C), 158.2 (C); HREIMS found *m*/*z* (M^+) 251.0955, $C_{16}H_{13}NO_2$ requires 251.0946. Lanthanide shifts induced by titration of both (−)-**2i** and (±)-**2i** (prepared from (±)-phenylglycinol) with a $CDCl_3$ solution of (+)-Eu(hfc)$_3$ (20 mol %) gave only one set of ^1H NMR signals for the optically active product (ee > 99%).

(5*S*)-5-Isopropyl-2-phenyl-5,6-dihydro-2*H*-1,4-oxazin-2-one (2j): yellow oil, 74%. $[\alpha]_D$ = +151.3° (*c* 1.08, $CHCl_3$); UV (acetonitrile) 264 (ϵ 6290), 328 nm (640); IR (NaCl, neat) 1738 (C═O), 1610 (C═N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (d, 3 H, *J* = 6.8 Hz), 1.15 (d, 3 H, *J* = 6.8 Hz), 2.01 (dq, 1 H, *J* = 6.8 Hz), 3.58 (ddd, 1 H, *J* = 9.7, 6.8, 4.0 Hz), 4.27 (dd, 1 H, *J* = 11.2, 9.7 Hz), 4.53 (dd, 1 H, *J* = 11.2, 4.0 Hz), 7.43 (m, 3 H), 8.00 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 19.0 (CH_3), 19.5 (CH_3), 30.6 (CH), 62.0 (CH), 68.5 (CH_2), 128.2 (CH), 128.6 (CH), 130.9 (CH), 134.2 (C), 155.4 (C), 157.4 (C); HREIMS found *m*/*z* 217.1103 (M^+), $C_{13}H_{15}NO_2$ requires 217.1103.

(5*R*)-3-(1-Naphthyl)-5-phenyl-5,6-dihydro-2*H*-1,4-oxazin-2-one (2k): yellow solid (93%); mp 155.5−156 °C; $[\alpha]_D$ = −276.2° (*c* 2.54, $CHCl_3$); UV (acetonitrile) 220 (ϵ 78220), 273 (5980), 278 nm (ϵ 5840); IR (NaCl, neat) 1739 (C=O), 1610 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.48 (dd, 1 H, *J* = 11.5, 10.6 Hz), 4.71 (dd, 1 H, *J* = 11.5, 4.4 Hz), 5.14 (dd, 1 H, *J* = 10.6, 4.4 Hz), 7.36 (m, 4 H), 7.50 (m, 3 H), 7.69 (d, 1 H, *J* = 7.1 Hz), 7.87 (m, 1 H), 7.93 (d, 1 H, *J* = 8.2 Hz), 8.04 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 60.6 (CH), 71.5 (CH_2), 124.6 (CH), 124.8 (CH), 126.1 (CH), 126.8 (CH), 127.1 (2 × CH), 128.1 (CH), 128.3 (CH), 128.6 (CH), 128.9 (2 × CH), 130.8 (CH), 130.9 (C), 132.0 (C), 133.6 (C), 136.4 (C), 155.2 (C), 161.1 (C); HREIMS found *m*/*z* 301.1105 (M^+), $C_{20}H_{15}NO_2$ requires 301.1103. Anal. Calcd for $C_{20}H_{15}NO_2$: C, 79.71; H, 5.02; N, 4.65. Found: C, 79.81; H, 5.06; N, 4.86.

(5*R*)-3-(2-Naphthyl)-5-phenyl-5,6-dihydro-2*H*-1,4-oxazin-2-one (2l): yellow solid (83%; R_f = 0.34, 3:7 ethyl acetate:hexane); mp 108−108.5 °C; $[\alpha]_D$ = −336° (*c* 4.96, $CHCl_3$); UV (acetonitrile) 221 (ϵ 61600), 261 (17200), 299 (12200), 343 nm (3100); IR (NaCl, neat) 1739 (C=O), 1603 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.21 (dd, 1 H, *J* = 11.3, 10.8 Hz), 4.55 (dd, 1 H, *J* = 11.3, 4.4 Hz), 4.95 (dd, 1 H, *J* = 10.8, 4.4 Hz), 7.34 (m, 5 H), 7.47 (m, 2 H), 7.84 (m, 3 H), 8.16 (dd, 1 H, *J* = 8.7, 1.7 Hz), 8.68 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 60.2 (CH), 71.1 (CH_2), 124.6 (CH), 126.4 (CH), 127.1 (2 × CH), 127.5 (CH), 127.6 (CH), 127.9 (CH), 128.1 (CH), 128.7 (2 × CH), 129.2 (CH), 130.3 (C), 131.1 (C), 132.5 (C), 134.4 (C), 136.8 (C), 154.9 (C), 157.8 (C); HREIMS found *m*/*z* 301.1103 (M^+), $C_{20}H_{15}NO_2$ requires 301.1103. Anal. Calcd for $C_{20}H_{15}NO_2$: C, 79.71; H, 5.02; N, 4.65. Found: C, 79.60; H, 5.11; N, 4.69.

(5*S*)-5-Isopropyl-3,4,5,6-tetrahydro-1,4-oxazin-2-one (4a). A solution of **2a** (0.100 g, 0.709 mmol) in ethyl acetate (4 mL) was hydrogenated (Pd−C, 10% w/w, 10 mg, 1 atm H_2) at room temperature for 4 h. Additional Pd−C (32.3 mg) was added and hydrogenation continued for another 3 h. The mixture was filtered through diatomaceous earth and the filter pad washed with ethyl acetate. Solvent was removed from the combined filtrate and washings to give morpholin-2-one **4a** as a yellow oil (80.4 mg; 79%; R_f = 0.18, ethyl acetate), pure by TLC and ^1H NMR. $[\alpha]_D$ = +15.5° (*c* 1.73, $CHCl_3$); UV (MeOH) λ 204 (ϵ 3290), 252 (330); IR (NaCl, neat) 3312 (NH), 1741 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (d, 3 H, *J* = 6.8 Hz), 0.94 (d, 3 H, *J* = 6.8 Hz), 1.62 (dq, 1 H, *J* = 6.8, 6.8 Hz), 1.74 (bs, 1 H), 2.69 (ddd, 1 H, *J* = 10.7, 6.8, 3.7 Hz), 3.56 (d, 1 H, *J* = 18.0 Hz), 3.72 (d, 1 H, *J* = 18.0 Hz), 4.10 (dd, 1 H, *J* = 11.0, 10.7 Hz), 4.36 (dd, 1 H, *J* = 11.0, 3.7 Hz); ^{13}C NMR ($CDCl_3$) δ 18.5 (CH_3), 18.6 (CH_3), 29.6 (CH), 47.7 (CH_2), 56.6 (CH), 72.5 (CH_2), 168.5 (C); HREIMS found *m*/*z* 143.0944 (M^+), $C_7H_{13}NO_2$ requires 143.0946.

(5*R*)-5-Phenyl-3,4,5,6-tetrahydro-1,4-oxazin-2-one (4b):[3] Compound **2b** was hydrogenated as above to obtain **4b** as yellow oil (quantitative); R_f = 0.39 (ethyl acetate); $[\alpha]_D$ = −91.6° (*c* 4.81, $CHCl_3$); UV (acetonitrile) λ 205 (ϵ 9090); IR (NaCl, neat) 3239 (NH), 1743 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.83 (d, 1 H, *J* = 17.8 Hz), 3.95 (d, 1 H, *J* = 17.8 Hz), 4.18 (dd, 1 H, *J* = 10.3, 3.7 Hz), 4.29 (dd, 1 H, *J* = 10.6, 10.3 Hz), 4.40 (dd, 1 H, *J* = 10.6, 3.7 Hz), 7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 48.1 (CH_2), 55.9 (CH), 74.1 (CH_2), 126.7 (CH), 128.2 (CH), 128.6 (CH), 137.4 (C), 167.6 (C); HREIMS found *m*/*z* 177.0785 (M^+), $C_{10}H_{11}NO_2$ requires 177.0790. Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.77; H, 6.26; N, 7.91. Found: C, 67.55; H, 6.25; N, 7.90.

(5*R*)-3-*tert*-Butyl-5-phenyl-3,4,5,6-tetrahydro-1,4-oxazin-2-one (4h). Compound **2h** (0.0214 g, 0.093 mmol) was dissolved in CH_2Cl_2 (1 mL). The flask was purged with N_2, and platinum(IV) oxide (14.7 mg) was added. The stirred mixture was hydrogenated for 3 h. After purging with N_2, the mixture was filtered through diatomaceous earth. Removal of the solvent gave **4h** as a white solid (21.4 mg, 99%; R_f = 0.32, 3:7 ethyl acetate:hexane). ^1H NMR showed a 13:1 mixture of diastereomers. Crystallization from ethyl acetate−hexane provided *a single diastereomer* (82%, de >99%): mp 111−112 °C; $[\alpha]_D$ = −76.4° (*c* 2.00, $CHCl_3$); IR (NaCl, neat) 3330 (NH), 1728 (C=O) cm^{-1}. ^1H NMR (C_6D_6) δ 1.04 (s, 9 H), 3.13 (s, 1 H), 3.54 (dd, 1 H, *J* = 10.3, 3.0 Hz), 3.72 (dd, 1 H, *J* = 10.3, 3.0 Hz), 3.85 (dd, 1 H, *J* = 10.3, 10.3 Hz); ^{13}C NMR ($CDCl_3$) δ 26.6 (CH_3), 36.3 (C), 56.6 (CH), 67.2 (CH), 74.3 (CH_2), 127.2 (CH), 128.6 (CH), 128.8 (CH), 138.3 (C), 168.9 (C); HREIMS found *m*/*z* 233.1416 (M^+), $C_{14}H_{19}NO_2$ requires 233.1416. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.16; H, 8.22; N, 6.00.

(3*S*,5*R*)-3,5-Diphenyl-3,4,5,6-tetrahydro-1,4-oxazin-2-one (4i). Compound **2i** was hydrogenated as described above for **4b** to obtain a mixture of diastereoisomers **4i** (4:1, ^1H NMR), oil (91%); R_f = 0.53 (1:1 ethyl acetate:hexane); UV (acetonitrile) 207 (ϵ 11900), 252 (350), 257 (370), 263 (290); IR (NaCl, neat) 3315 (NH), 1743 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.60 (bs, 1 H), 4.36 (m, 3 H), 4.79/4.91 (s, 1 H), 7.36 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 52.0/57.4 (CH), 60.3/64.0 (CH), 73.8/74.8 (CH_2), 126.8/127.0 (CH), 127.2/128.1 (CH), 128.3/128.4 (CH), 128.6 (CH), 128.8 (2 × CH), 137.4/137.9 (C), 138.0/138.1 (C), 168.3/168.9 (C); 126.8−128.8 several signals; HREIMS found *m*/*z* (M^+) 253.1109, $C_{16}H_{15}NO_2$ requires 253.1103.

Dimeric Products, 5f and *epi*-5f, from SeO_2 Oxidation of 1f. A solution of **1f** (0.400 g, 2.84 mmol) in dioxane (7 mL) was added to selenium dioxide (0.70 g, 6.3 mmol) suspended in dioxane (7 mL). The mixture was stirred and heated under reflux (1 h), cooled, and filtered through silica gel with 1:1 ethyl acetate:hexane. Removal of solvent under reduced pressure gave a reddish-brown oil (0.250 g) which was separated by chromatography (silica gel, gradient, 1:4 to 3:1 ethyl acetate:hexane) to afford of **5f** (86.5 mg, 20%) and *epi*-**5f** (91.6 mg, 21%).

5f: solid; $[\alpha]_D$ = +33.0° (*c* 1.09, $CHCl_3$); UV (acetonitrile) λ 286 (ϵ 12700), 314 nm (13500); IR (NaCl, neat) 3293 (weak), 1742, 1685, 1616 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (d, 3 H, *J* = 6.8 Hz), 0.97 (d, 3 H, *J* = 6.7 Hz), 1.12 (m (overlapped d and t), 6 H), 1.89 (dq, 1 H, *J* = 6.7 Hz), 2.34 (q, 2 H, *J* = 7.5 Hz), 2.44 (septet, 1 H, *J* = 6.9 Hz), 3.12 (m, 1 H), 4.08 (dd, 1 H, *J* = 11.4, 7.4 Hz), 4.20 (dd, 1 H, *J* = 11.4, 4.1 Hz), 4.80 (s, 2 H), 7.11 (d, 1 H, *J* = 13.4 Hz), 7.99 (bt, 1 H, *J* = 9.7 Hz); ^{13}C NMR ($CDCl_3$) δ 9.0 (CH_3), 18.1 (CH_3), 19.4 (2 × CH_3), 19.5 (CH_3), 27.4 (CH_2), 30.1 (CH), 34.0 (CH), 64.1 (CH), 65.0 (CH_2), 66.8 (CH_2), 104.6 (C), 152.2 (CH), 155.8 (C), 163.5 (C), 174.1 (C); HREIMS found *m*/*z* 310.1885 (M^+), $C_{16}H_{26}N_2O_4$ requires 310.1893.

epi-**5f:** solid; $[\alpha]_D$ = +6.0° (*c* 0.58, $CHCl_3$); UV (acetonitrile) λ 312 nm (ϵ 19800); IR (NaCl, neat) 3318 (weak), 1739, 1702, 1621 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (d, 3 H, *J* = 6.8 Hz), 0.99 (d, 3 H, *J* = 6.8 Hz), 1.14 (m, (overlapped d and t), 6 H), 1.92 (dq, 1 H, *J* = 6.7 Hz), 2.36 (q, 2 H, *J* = 7.6 Hz), 2.50 (septet, 1 H, *J* = 6.9 Hz), 3.26 (m , 1H), 4.18 (m, 2H), 4.83 (s, 2 H), 5.80 (bt, 1 H, *J* = 11.5 Hz), 7.39 (d, 1 H, *J* = 13.5 Hz); ^{13}C NMR ($CDCl_3$) δ 9.0 (CH_3), 18.2 (CH_3), 19.4 (CH_3), 19.5 (2 × CH_3), 27.5 (CH_2), 30.3 (CH), 34.0 (CH), 63.1 (CH), 65.0 (CH_2), 67.2 (CH_2), 104.9 (C), 144.5 (CH), 158.9 (C), 162.0 (C), 174.2 (C); HREIMS found *m*/*z* 310.1882 (M^+), $C_{16}H_{26}N_2O_4$ requires 310.1893.

(4*S*)-4-Isopropyl-2-oxazolidinone (6). A solution of **1a** (0.298 g, 2.35 mmol) in dry pyridine (6 mL) was added to SeO_2 (0.576 g, 5.20 mmol) in pyridine (6 mL) and the mixture heated at reflux (1 h), cooled, and eluted through silica gel with 1:1 ethyl acetate:hexane. The brown residue (0.1094 g) obtained by removal of solvent under vacuum was purified by chromatography (silica, gradient from 1:9 ethyl acetate:hexane to ethyl acetate) to afford the known oxazolidinone **6** as a yellow oil (32.8 mg, 11%):[9] IR (NaCl, neat) 3275 (NH), 1748 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (d, 3 H, *J* = 6.8 Hz), 0.94 (d, 3 H, *J* = 6.8 Hz), 1.71 (dq, 1 H, *J* = 6.8, 6.8 Hz), 3.59 (m, 1 H), 4.08 (dd, 1 H, *J* = 8.7, 6.3 Hz), 4.42 (dd, 1 H, *J* = 8.7, 8.7 Hz), 6.85 (bs, 1 H); ^{13}C NMR ($CDCl_3$) δ 17.6 (CH_3), 17.9 (CH_3), 32.6 (CH), 58.4 (CH), 68.6 (CH_2), 160.5 (C).

(3*S*,5*S*)- and (3*R*,5*S*)-3-Methoxy-5-isopropyl-3,4,5,6-tetrahydro-1,4-oxazin-2-one (7). 5,6-Dihydro-2*H*-oxazin-2-one **2a** (0.0422 g, 0.299 mmol) was heated in methanol (1.5 mL, 37.0 mmol) at reflux (6 h). Removal of the solvent under reduced pressure afforded **7** as a 1:1 mixture of C3 epimers (yellow oil, 0.0497 g, 96%; R_f = 0.48, ethyl acetate): UV (hexane) λ 202 (ϵ 1520), 220 (540); IR (NaCl, neat) 3311 (NH), 1750 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (d, 3 H, *J* = 6.7 Hz), 0.93 (d, 3 H, *J* = 6.7 Hz), 1.04 (d, 3H, *J* = 6.7 Hz), 1.08 (d, 3 H, *J* = 6.7 Hz), 1.64 (dq, 2 × 1 H, *J* = 6.7, 6.7 Hz), 2.20 (bs, 1 H), 3.00 (m, 1 H), 3.18 (ddd, 1 H, *J* = 7.5, 7.5, 7.5 Hz),

3.32 (m, 1 H), 3.42 (t, 1 H, J = 7.5, 7.5 Hz), 3.77 (s, 3 H), 3.80 (s, 3 H), 3.95 (m, 1 H), 4.05 (t, 1 H, J = 7.5, 7.5 Hz), 4.87 (s, 1 H), 5.04 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.4/19.6 (CH_3), 20.0/20.3 (CH_3), 31.2/31.4 (CH), 52.0/52.2 (CH_3), 63.8/65.5 (CH), 69.7/69.8 (CH_2), 88.0/88.2 (CH), 169.9/170.3 (C); HREIMS found m/z 173.1042 (M^+), $C_8H_{15}NO_3$ requires 173.1052.

(4*S*)-4-Isopropyl-2-benzoyl-3*H*-1,3-oxazolidine (8). A solution of phenylmagnesium bromide in THF (1 M, 3.0 mL, 3.0 mmol) was added dropwise to a stirred solution of **2a** (0.401 g, 2.85 mmol) in dry THF (15 mL) at −78 °C. The reaction was quenched at −78 °C after 20 min by the addition of $NaHCO_3$ (aqueous, saturated, 2.5 mL). The reaction mixture was diluted with ethyl acetate (50 mL) and H_2O (10 mL), and the layers were separated. The aqueous layer was extracted with 3 × 75 mL of ethyl acetate. The combined organic layers were dried ($MgSO_4$), and the solvent was removed to give a yellow oil (0.567 g) consisting of a 1:1 epimeric mixture of the sensitive product **8** (57%, by NMR); R_f = 0.74 (1:1 ethyl acetate: hexane). Silica gel chromatography provided pure **8** accompanied by substantial loss of material through decomposition: colorless oil; UV (MeOH) λ 247 (ϵ 8360), 287 (2170); IR (NaCl, neat) 3305 (NH, weak), 1692 (PhC=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.91 (d, 3 H, J = 6.7 Hz), 0.95 (d, 3 H, J = 6.7 Hz), 1.04 (d, 3 H, J = 6.6 Hz), 1.13 (d, 3 H, J = 6.6 Hz), 1.68/1.70 (dq, 1 H, J = 6.6 Hz), 2.90 (bs, 1 H), 3.13 (m, 3 H), 3.62 (dd, 1 H, J = 7.9, 6.2 Hz), 3.92 (dd, 1 H, J = 7.9, 6.8 Hz)/3.98 (dd, 1 H, J = 6.8, 5.9 Hz), 5.60/5.62 (s, 1 H, H2), 7.53 (m, 3 H), 8.10 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 19.4/19.9(CH_3), 20.0/20.6 (CH_3), 31.3 /31.9 (CH), 64.1/65.8 (CH), 69.9/70.0 (CH_2), 89.2/89.4 (CH), 128.5 /128.6 (2 × CH), 129.3 /129.4 (2 × CH), 133.6 /133.9 (CH), 134.2/134.3 (C), 193.6/194.3 (C=O); HREIMS found m/z 219.1252 (M^+), $C_{13}H_{17}NO_2$ requires 219.1259.

(*S*)-*tert*-Leucine Hydrochloride (10). A solution of morphilinone **4h** (0.0195 g) in ethanol (10 mL) was saturated with dry HCl and then heated at reflux for 16 h, cooled, and concentrated under vacuum to a yellow oil (35.8 mg). The residue was dissolved in $CHCl_3$, reevaporated, and dissolved in ethanol (10 mL). Pd−C (10% w/w, 13.1 mg) was added and the mixture hydrogenated (25 °C, 1 atm H_2) for 5 h. After the mixture was filtered through diatomaceous earth, the filtrate was concentrated to an off-white solid which was dissolved in water and extracted once with ether.[3] The ether layer was back-extracted with water, and the combined aqueous layers were diluted with ethanol and concentrated under vacuum to give of an off-white solid (11.7 mg). The residue was dissolved in 6 M HCl aqueous (2 mL) and heated in a sealed tube (110 °C) for 26 h. After cooling to room temperature, the volatiles were removed from the mixture to give a pale-yellow solid (11.2 mg) which was eluted through a short charcoal column with water. Removal of water gave pure (S)-*tert*-leucine hydrochloride (**10**, white solid, 10.5 mg, 75% for three steps), which was identical with an authentic sample by ^{1}H NMR, $[\alpha]_D$ and TLC (R_f = 0.43, 3:1:1 *n*-BuOH:AcOH:H_2O). A portion of the product (*ca.* 0.5 mg) was treated with 1-fluoro-2,4-dinitrophenyl-5(*S*)-alaninamide (FDAA) according to Marfey[20] as were authentic (*S*)-(−)-**10** and (±)-**10**, and the FDAA adducts were analyzed by diode array HPLC (4.6 mm × 150 mm RP18 column, 1.5 mL min^{-1}, elution with a linear gradient; buffer A, 90% 0.05 M triethylamine phosphate, B, 10% acetonitrile, to 10% buffer A over 30 min) and UV monitoring at λ 340 nm. Synthetic (S)-*tert*-Leucine FDAA adduct eluted at 18.1 min, and no adduct was detected from (*R*)-*tert*-leucine (20.1 min).

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Supporting Information Available: Copies of ^{1}H NMR and ^{13}C NMR spectra of **1h,k−l, 2a−d,g−l, 4a,b,h,i,** and **6−8** and ^{1}H NMR of (−)-**2i** and (±)-**2i** (43 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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